REMARKS

Rejection of the claims under 35 USC §102:

Claims 1-9 and 11-17 have been rejected under 35 U.S.C. 102(b) as being anticipated by Stedman et al (WO 99/31982, 1999). Applicants have amended the claims to more distinctly differentiate their method from the method taught by Stedman. Claim 1 has been amended to cite delivery of a viral vector to extravascular limb muscle cells and incorporates limitations from claims 11 and 12. Support for the amendments can be found in the specification on page 3 lines 7-13, page 7 lines 16-32, page 15 lines 5-8 and page 21 lines 17-19. For delivery of adenovirus to limb muscle cells, the method of Stedman requires either: a) injection of both histamine and papaverine (series J, Table 1, page 60); or, b) perfusion of the limb, with a solution containing either a vascular permeability-enhancing agent (e.g. histamine) or a vasodilating agent (e.g. papaverine), for 45 minutes under pressure followed by removal and flush of the injection solution (series K, Table 1). Perfusion requires accessing both an artery and a vein and circulating fluid though the limb using a pump (see FIG. 7). Still, Stedman observed only weak delivery to limb muscle cells unless both histamine and papaverine were injected, multiple tourniquets were applied, and venous drainage and venorrhaphy were performed (series M, Table 1). In contrast, Applicants' process requires only injection of fluid containing the virus into a limb artery (examples 1, 2, 3, 5) or vein (examples 4, 6, 8, 9, 10), does not require injection of a vascular permeability-enhancing agent or a vasodilating agent to achieve delivery (page 6 lines 16-22, and attached declaration under 37 CFR 1.132) and permits blood flow to the limb to be restored within 2 minutes of injection of the virus (page 7 lines 20-24 and examples). Stedman does not teach injection of a viral vector in a large volume.

Applicants have demonstrated delivery of naked DNA and non-viral DNA complexes without co-administration of papaverine or histamine (examples 5, 6, 8, 9). Applicants submit, with this paper, a declaration under 37 CFR 1.132 showing delivery of adeno-associated virus to limb skeletal muscle cells in mouse and rat without injection of either papaverine or histamine or other vasodilating compound. The examples were performed as described in the specification in example 4, except that no papaverine was injected.

The action states, on page 2 that Stedman teaches increasing vessel permeability by providing virus vector suspension continuously at high pressure. It is the Applicants' understanding of the teaching of WO 99/31982 that Stedman injects virus in a low volume followed by injection of a chase volume and perfusion under pressure. "In yet another aspect, the method further comprises the step of increasing the perfusion pressure within the vessel above the normal physiological perfusion pressure after providing the macromolecular assembly to the vessel." (page 10 lines 23-25) and "In a variation of the method of the invention, the perfusion pressure within the blood vessel is increased above the normal physiological perfusion pressure after providing the gene vector to the vessel. The increase in perfusion pressure may be within the range from 5 to 80 pounds per square inch or more. However, it is recognized that the greater the increase in perfusion pressure, the greater is the risk of structural damage to vascular and extravascular tissues. It is contemplated that in situations in which a blood vessel has been isolated from the blood circulatory system of a mammal, and particularly from the mammal's heart, the risk of injury to the mammal is less dependent upon the increase in perfusion pressure, compared with the situation in which the blood vessel is not so isolated." (page 31 lines 17-28). Furthermore, the pressures indicated by Stedman are not indicative of the in vivo pressures in the mammal. Stedman provides no indication of what high pressure, medium pressure or low pressure is in the vascular beds of the mammal. "Owing to the outflow resistance of the micropipettes and microcannulae used to administer AdCMVlacZ in these experiments, it is understood that applied infusion pressures are always much higher than the pressures achieved in the vascular beds." (page 54 lines 3-6). In fact, Stedman states, "Intravascular delivery of adenovirus vector was not significantly improved by applying supraphysiologic perfusion pressures simultaneously with vector administration to increase Starling forces in favor of transudation, as indicated by the staining pattern depicted in Figure1b and by the data presented in Table 1." (page 58 lines 26-29). In contrast Applicants method increases volume/pressure in the mammal through injection of a solution containing the virus, does not require perfusion, and does result in delivery of virus to extravascular cells. Stedman further states that if the endothelium of muscle suddenly becomes permeable to albumin-sized molecules, circulatory collapse ensues in the absence of extracorporeal circulatory support (page 23 lines 6-15). Applicants' method does not provide extracorporeal circulatory support, but does not cause significant toxic effects.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1-9, 11-13, 15 and 16 should be allowable. Applicants respectfully request a timely Notice of Allowance be issued in the case.

Respectfully submitted,

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